TREATMENT OF SEVERE DEPRESSION BY IMIPRAMINE (TOFRANIL)

AN INVESTIGATION OF 100 CASES

By

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THE depressive syndrome is very distressing and incapacitating for any patient who suffers from it, and wherever it occurs psychiatrists are faced with a serious problem more particularly because of the consequent risk of suicide. The incidence of depressive illnesses has in my experience certainly not decreased during recent years, on the contrary it has probably increased and there is still an urgent need for more effective therapy to counteract the dire suffering and suicidal rate involved.

PSYCHOPHARMACOLOGY

This word is assuming increasing significance and importance for the clinical psychiatrist. During the last 10 years twenty-eight different chemicals (each with a proprietary name of its own) with tranquillizing and sedative effects on the nervous system, and five with stimulant ones have been introduced into the pharmacological field. None of these had a specific anti-depressant effect until the advent of imipramine (an amino-di-benzyl derivative, see Fig. 1)

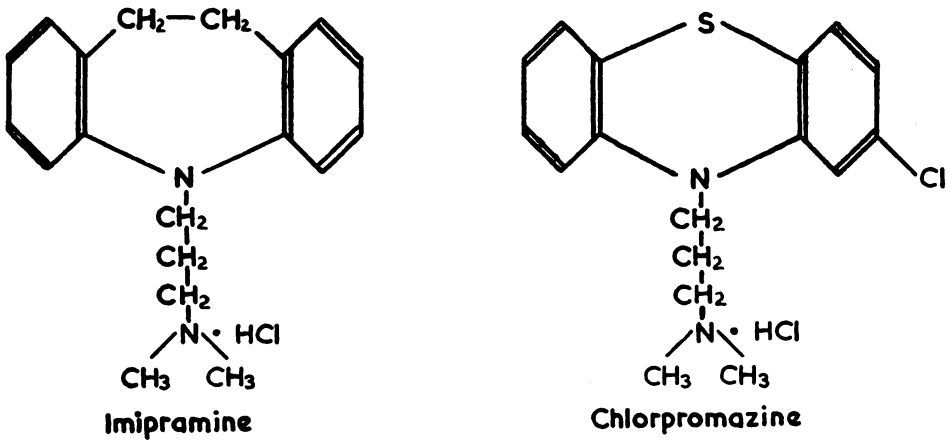

FIG. 1

a few years ago (Lehmann, 1958). This drug originated in Switzerland where the preliminary pharmacological and clinical investigations were made. Kuhn (1957) published the first paper on its clinical effects and since then other papers have appeared in Canada, the U.S.A., and Italy. The drug has only recently

become available in this country and this article describes a clinical investigation of its potentialities.

The discovery of convulsive therapy presented to psychiatry the first efficacious method of treating the depressive illnesses and up to date it has held almost a monopoly in successful results. The use of drugs in the treatment of depression other than neurotic depression has, in my opinion, been disappointing and seldom fundamentally successful, and this opinion is shared by probably the majority of clinical psychiatrists (see Kuhn, 1958, etc.). Amphetamine and Dexedrine stimulate cortical activity without counteracting the basic depressive processes and are drugs of addiction. Drinamyl (a combination of amphetamine and sodium amytal) is not radically effective, nor are pipradrol (Meratran) and methyl phenedyl acetate (Ritalin), chlorpromazine (Largactil) and the other phenothiazine derivatives (Stelazine and Fentazin, etc.) are almost useless except in schizophrenic depression. Reserpine (Serpasil) may aggravate depression and is strongly contra-indicated in its treatment.

Despite the efficacy of E.C.T. in most cases of depression it has certain disadvantages which have spurred on the search for a psychopharmacological agent, viz.: (1) the elaborate technique involved and well-known dangers such as laryngeal spasm when Pentothal is used in the "modified" procedure, (2) such complications as memory defect and a sense of fear for the treatment, (3) the difficulties of arranging maintenance E.C.T., (4) certain patients are physically unfit for this form of treatment.

There is a general consensus of opinion amongst psychiatrists abroad who have published papers on imipramine that this drug counteracts and dispels depression in a different and more potent manner than any drug manufactured hitherto. The present work was undertaken largely with the objective of confirming or refuting their claims.

Clinical Investigation of Imipramine (Tofranil)

In effecting a clinical investigation of any drug one endeavours to reach conclusions regarding (1) its clinical effects and the indication for its use, (2) the optimum dosage and method of medication, and (3) its side-effects and their management.

The diagnosis of depression in the psychiatric sense is based on a syndrome of symptoms of which the all-important ones are:

1. The subjective feeling of depression itself with its concomitant feelings of sadness, despondency, hopelessness, and misery.
2. Negative thinking.
3. Lack of mental energy and initiative and feelings of fatigue.
4. Anorexia and insomnia.

This constant picture is varied by the presence or absence of both or either:

(*a*) Ideas or delusions of guilt and unworthiness.

(*b*) Mental agitation.

The classification of depressive illnesses still varies greatly from one author to another (see references). I have divided the present series of cases into the following categories:

(a) *Manic Depressive.* Patients qualify for this group by virtue of a cyclothymic extroverted temperament and personality, previous typical attacks, a family history of this illness, etc.

(b) *Endogenous*. Cases suffering from their first attack and whose personality traits and previous history did not qualify them definitely for the manic depressive group. In these cases an obvious physical or mental precipitating factor was present and they were subgrouped accordingly as puerperal, menopausal, post-hysterectomy, post-influenzal and endogenous-reactive (i.e. a mental reactive factor).

(c) *Senile Arteriosclerotic*. In these patients a depressive syndrome occurred for the first time in senile patients with arteriosclerosis and some degree of dementia. Senile patients without obvious dementia and arteriosclerosis were placed in the manic depressive or endogenous group.

(d) *Psychoneurotic*. The depressive syndrome occurring in patients definitely suffering from a psychoneurosis.

(e) *Psychopathic*. A depressive syndrome occurring in a psychopathic personality.

(f) *Schizo-affective*. Depression occurring in the group of psychotic patients who occupy a borderline between a schizophrenic and manic depressive state.

The use of rating scales is of dubious validity in presenting results. Straker (1959) considers them unwieldy and prone to add confusion to the results offered. I believe that the syndrome of depressive symptoms described above is an interdependent entity and that the symptoms improve or deteriorate together and not in measurably differing degrees.

Tuteur (1956) has called attention to the pitfalls and limitations of the "blind" and "double-blind" techniques of control involving the use of placebos and neither technique was used in this investigation. However, certain controls were implicit (see below).

Paul Hoch (1958) has stated: "Regardless of the methods you use today in psychiatry to observe behaviour changes, the only method which can be used, despite its many shortcomings, is the clinical one. Any attempt to replace it in the present state of our knowledge by all kinds of so-called scientific constructs is doomed to failure."

This is a clinical investigation and the results are graded on clinical criteria as follows:

1. *Recovery*. A recovery from the depressive syndrome of symptoms (including agitation and ideas and delusions of guilt and unworthiness) and from the debility associated with them. A return to pre-depressive activity and work.
2. *Much Improvement*. The distress and debility resulting from the depressive syndrome is greatly reduced and the patient is able to live at home or in an open ward of the hospital to perform useful work despite the persistence of depressive symptoms in mild intensity.
3. *Improved*. An improvement in depressive symptoms and although the depression is still present and so debilitating that the patients have to remain under constant nursing supervision.
4. *Unchanged*. No appreciable change in the depressive symptoms.
5. *Worse*. A deterioration in depressive symptoms due directly to the drug, or the development of mental side-effects necessitating withdrawal of the drug.

Material and Method

The hundred patients involved in this investigation were all women, and all in-patients in St. Bernard's Hospital. Details of their age groups, etc., are shown in Table I.

TABLE I

Details of Case Material

Age Groups		Duration of Depression Before Treatment by Tofranil	
Under 20	1	Less than one month	6
21–30	9	1– 2 months	10
31–40	14	2– 3 months	12
41–50	20	3– 4 months	9
51–60	23	4– 5 months	8
61–70	20	5– 6 months	5
71–80	11	6–12 months	12
81–90	1	1– 2 years	16
Over 90	1	2– 3 years	10
	—	3– 4 years	4
	100	4– 5 years	3
	—	5–10 years	3
		Over 10 years	2
			—
			100
			—

Previous Attacks		
0	43	
1	27	
2	14	
3	8	
More than 3	8	(2=over 10)
	—	
	100	
	—	

Attempted Suicide		Method			
(*a*) During present attack	25	Barbiturates	8	Thawpit	1
			2	Jeyes Fluid	1
(*b*) During previous attacks	7	Aspirin	3	Cut throat	2
		Largactil	1	Gas	6
		Tofranil	1		

The material covered all types of depression typical to an ordinary mental hospital, from the most chronic recalcitrant cases to recent cases with a good prognosis. As in-patients they were, of course, all cases of severe depression, twenty-five having made serious attempts at suicide before admission, and most of the others being potentially suicidal on admission.

The first cases to be treated were the most chronic ones and the results were so favourable that the drug was then used on recent patients.

In order to obtain an assessment of the value of imipramine the investigation was undertaken from four different viewpoints:

1. Patients who were unsuitable for E.C.T. for one of the following reasons were treated with imipramine: (*a*) physically unfit, (*b*) cases in whom E.C.T. had to be terminated before any appreciable improvement had taken place because of laryngeal spasm, difficult veins, memory defect, or the patient having developed such fear or dislike for the treatment that she refused to have any more.

2. Cases who were still in hospital because their condition had failed to respond to E.C.T. and other treatments with more than transient improvement.

3. Recurrent cases who had been treated with E.C.T. during previous admissions were on their present re-admission treated by imipramine instead of E.C.T.

4. Patients experiencing their first severe attack of depression and this being their first admission to a mental hospital were treated with imipramine (instead of E.C.T.) from the beginning.

The method of prescribing this drug has varied from one psychiatrist to another. Some advocate a rapid increase of dosage over a short period followed by a reduction within a short period. In all the present series of cases 25 mg. t.d.s. was prescribed in the first instance. This dose was sufficient to produce recovery in some cases. Once the patient ceased improving on this dose over a period of a few days the dose was increased to 50 mg. t.d.s. and those who did not recover on this and who tolerated the drug well were in turn increased to 75 mg. t.d.s. and where necessary 100 mg. t.d.s. The dose was never raised beyond this level. In no instance were injections used nor was the practice advocated by some writers of rapidly increasing the dosage during the first few weeks and then gradually reducing it ever resorted to.

No cases were included in the series who had been treated and followed up for less than three months and none have yet been treated and followed up for more than nine months. Once the maximum effect of the drug had been obtained maintenance doses were continued. I decided in view of the marked liability for a relapse in cases of this type to err on the side of caution and to continue with the optimum dose for at least eight weeks after its maximum effect. Thereafter the dose was very gradually reduced. In twelve particularly severe or recalcitrant cases it was deemed necessary to give a few E.C.T. treatments while continuing as usual with the imipramine (Tofranil). Collective details of the treatment are presented in Table II.

TABLE II

Details of Treatment

Number Who had Received E.C.T. Prior to Imipramine

Treatment

Maximum dose given:	
25 mg. t.d.s.	22
50 mg. t.d.s.	45
75 mg. t.d.s.	22
100 mg. t.d.s.	11

Duration of Treatment

6 weeks–2 months	23
2–3 months	37
3–4 months	27
Over 4 months	13

Number of Cases Receiving E.C.T. During Imipramine Treatment—12

No. of E.C.T.s Given	No. of Patients
2	2
3	3
4	2
5	5

Careful observation was kept on all cases for any side-effects from the drug. Blood pressure readings were made twice a day and routine blood counts taken.

The same occupational and recreational regime nursing care and psychiatrist's supervision were available to these patients as to patients treated

by E.C.T. or other methods. Everything possible was done to help all patients to cope with any social, marital, or other problems confronting them. Thus a broadly constant environment was afforded as a control for comparing results of imipramine (Tofranil) treatment with E.C.T. and other treatments.

Results

(a) *Percentages.* The grading of results was made on the criteria already mentioned. Table III represents the total results obtained in each type of

Table III

Showing the Therapeutic Effect of Imipramine on 100 Cases of Depression

Type of Depression	Re-covery	Much Im-proved	Im-proved	No Change	Worse	Totals
Manic-depressive ..	34	7	3	2	2	48
Endogenous ..	19	3	–	–	–	22
Arteriosclerotic ..	6	4	3	1	1	15
Psychoneurotic ..	—	3	2	4	1	10
Psychopathic ..	—	1	1	–	–	2
Schizo-affective ..	—	2	–	1	–	3
Totals ..	59%	20%	9%	8%	4%	100

depression and in the full 100 cases. Of the 22 endogenous cases, eight were menopausal, three puerperal, two post-hysterectomy, two post-influenzal, and seven endogenous-reactive cases.

All cases in the "recovery" group have gone home well and free from depression, and it is likely that some cases in the "much improved" group of the manic-depressive and particularly the endogenous types will before long also grade to "recovery".

The cases in the "improved" and "no change" categories had been depressed for many months or years and had a bad prognosis, apart from two cases whose treatment had to be terminated because of side-effects too soon to produce any appreciable change in their depression.

In the arteriosclerotic group the results of treatment are assessed entirely upon its effect on the depression present. Needless to say, the degree of dementia was unaffected.

The comparatively poor results obtained in the psychoneurotic group were, in my estimation, to be expected in view of many years' experience of the treatment of such cases with E.C.T. The fact that the emphasis in the origins of such depressions is on the psychopathological rather than the endogenous factor probably accounts for this. The cases who failed to respond at all had suffered from a chronic neurosis for several years of such intensity as to necessitate hospitalization during most of that time.

The "much improved" psychopath responded by disappearance of her depression but was not placed in the "recovery" group because of the probability of a relapse and because her other symptoms have prevented her discharge from hospital.

The results obtained in two (much improved) of the three schizo-affective patients were really remarkable. These cases had defied all other treatments (i.e. E.C.T., chlorpromazine, trifluoperazine, etc.), but on imipramine their condition steadily improved until they are now better than since admission to hospital, free from depression apart from occasional short bouts, going

home for weekends, and apparently, contrary to all previous expectations, going to be fit for discharge home in the near future (Case No. 10).

The results were also analysed from the four viewpoints mentioned above.

1. Eighteen patients were unsuitable for E.C.T., eight being physically unfit (one auricular fibrillation, one recent stroke, one retro-peritoneal sarcoma, and five hypertensions (B.P. 240, 234, etc.)), two having had laryngeal spasms, one with difficult veins, two with severe memory defect, and four being afraid and refusing E.C.T. treatment. They had been in hospital for periods varying from a few months to a few years before imipramine treatment. The beneficial results obtained in this group were beyond any expectation (Table IV) and indicate that imipramine has a valuable place in the treatment of depressive cases unsuitable for E.C.T.

TABLE IV

Response of Cases Unfit for E.C.T. to Imipramine

Groups	Recovery	Much Improved	Improved	No Change	Worse	Totals
Manic-depressive ..	7	0	0	0	0	7
Endogenous ..	3	1	0	0	0	4
Arteriosclerotic ..	3	2	2	0	0	7
Psychoneurotic ..	–	–	–	–	–	–
Psychopathic ..	–	–	–	–	–	–
Schizo-affective ..	–	–	–	–	–	–
Totals	13	3	2	0	0	18

2. Although the majority of depressive illnesses respond to E.C.T. in every hospital there are a number who fail to do so sufficiently for discharge and remain chronically hospitalized for an indefinite period. Of the 800 female patients under my supervision in St. Bernard's Hospital, 29 were found to be in this category. Seventeen of these patients had been in hospital for periods of several months but less than one year. Of the 12 who had been in for over a year, 2 had been in hospital for 2 years, 4 had been for 3 years, 1 for 4 years, 1 for 5 years, and 4 for 6 years.

The results of imipramine on these 29 cases as opposed to those of previous E.C.T., etc., are shown in Table V. They are impressive and show that in certain cases imipramine may produce better results than E.C.T. One case responded to a combination of imipramine and E.C.T. who had not done so to either alone. It was this result which encouraged us to use E.C.T. in cases in groups (3) and (4).

TABLE V

The Effect of Imipramine on Cases who had Failed to Recover on E.C.T.

	Effect of E.C.T.				Effect of Imipramine				
Type	Recovery	Much Improved	Improved	No Change	Recovery	Much Improved	Improved	No Change	Totals
Manic-depressive	–	1	6	6	5	3	3	2	13
Endogenous ..	–	2	4	–	6	–	–	–	6
Arteriosclerotic	–	–	–	2	–	–	1	1	2
Psychoneurotic	–	–	1	3	–	1	–	3	4
Psychopathic ..	–	–	–	1	–	–	1	–	1
Schizo-affective	–	–	1	2	–	2	–	1	3
Totals ..	0	3	12	14	11	6	5	7	29

3. Twenty-six cases of this series suffered from recurrent depressive states and were re-admitted during the period of this investigation. They were treated immediately by imipramine instead of by E.C.T. as they had been on previous admissions. Table VI shows the results obtained.

TABLE VI

Re-admissions Treated with E.C.T. on Previous Admissions now Treated with Imipramine

	Recovery	Much Improved	Improved	No Change	Worse	Total
Manic-depressive ..	16	4	–	–	2	22
Endogenous ..	1	–	–	–	–	1
Arteriosclerotic ..	–	1	–	–	1	2
Psychoneurotic ..	–	–	1	–	–	1
Psychopathic ..	–	–	–	–	–	–
Schizo-affective ..	–	–	–	–	–	–
Totals ..	17	5	1	–	3	26

The three patients who are registered in the worse category were worse not because of worse depression but because they became so agitated and distressed that imipramine treatment had to be terminated within a few days.

The psychoneurotic case was a very chronic case and E.C.T. on the previous admission had also only produced "improvement". The arteriosclerotic case was aged 77 and again E.C.T. had previously produced no better result than imipramine on this occasion.

Of the four "much improved" cases one was a case chronically maladjusted to life and with a bad prognosis. E.C.T. given for her depression (as an out-patient) had also failed to dispel the depression completely. One case who had "recovered" on imipramine and was about to go home developed purpura and on withdrawal of the drug relapsed and then settled in the "much improved" grade.

Four cases with very severe and distressing depression responded so sluggishly to imipramine that E.C.T. was introduced. They all recovered after very few E.C.T.s—one had two treatments, two had three, and one had five.

These results point to imipramine being as effective as E.C.T. in many cases of recurrent depression although a few cases prove unsuitable because of severe side-effects and some require E.C.T. in combination with the drug in order to accelerate recovery.

4. Twenty-seven first admissions were treated with imipramine instead of E.C.T. as they would have been in ordinary circumstances. The results are presented in Table VII.

TABLE VII

First Admissions Treated with Imipramine

	Recovery	Much Improved	Improved	No Change	Worse	Totals
Manic-depressive ..	5	1	–	–	–	6
Endogenous ..	10	1	–	–	–	11
Arteriosclerotic ..	3	1	–	–	–	4
Psychoneurotic ..	–	2	1	1	1	5
Psychopathic ..	–	1	–	–	–	1
Schizo-affective ..	–	–	–	–	–	–
Totals ..	18	6	1	1	1	27

It is probable that the manic-depressive case who is "much improved" will, in due course, recover, and the endogenous case in that grade did "recover" and went home but has recently shown some symptoms of relapse and is, therefore, graded as "much improved". The dose of imipramine has been raised again, and it is expected she will recover again. The psychopathic case "recovered" from her depression but because of other psychopathic symptoms remained in hospital and was, therefore, graded "much improved".

Seven of this group were given some E.C.T. during imipramine treatment. This was considered necessary because their distressing symptoms did not yield rapidly to the drug. One was a severe psychoneurotic, four endogenous cases, and two manic depressives. One had two treatments, one had three, two had four, and two had five. All recovered except the psychoneurotic who was "much improved".

The psychoneurotic case labelled "worse" developed hallucinosis and the drug had to be withdrawn.

The figures for this group reveal that imipramine alone was successful in the treatment of the majority of depressive cases on their first admission but that E.C.T. was required in combination in some very severe cases who did not respond rapidly to imipramine alone.

It is worthy of note that all cases graded as "recovery" were very gradually weaned off the drug over a period of several weeks and so far none of them has relapsed into depression although they have been out of hospital for periods varying from three to six months.

(b) *Individual Cases.* The true potentialities of this drug can only be fully appreciated by direct observation of its effects but are further illustrated by reports of individual cases. The following are a few brief case histories:

Case No. 1. Age 67. History of 10 years fluctuating but continuous depression. Admitted 17 April, 1958. Developed laryngeal spasm from E.C.T. after 11 E.C.T. treatments had produced no improvement. Imipramine (Tofranil) started in February, 1959, in 50 mg. t.d.s. doses produced a recovery now retained for 5 months.

Case No. 2. Age 68. Previous attack 1953, attempted suicide. Admitted 1 June, 1959, after being in bed one month at home. Auricular fibrillation and old T.B. prevented E.C.T. Good and rapid response to imipramine. Much improved within four weeks. Home, recovered, two weeks later. Is still free from depression—3 months.

Case No. 3. Age 27. Three children: 3 years, 2 years, and 1 year old. Never mentally her usual self since birth of last child. Admitted very depressed having attempted suicide with aspirins. Given E.C.T., hated it and refused more after 5th treatment. Slightly improved. Put on imipramine (Tofranil). Maximum dose 50 mg. t.d.s. Further improvement within a few days and then a rapid recovery. Home for last 4 months.

Case No. 4. Age 46. Admitted 8 January, 1959. Suffering from severe depression with pronounced paranoid symptoms (no previous attacks). Menopausal. E.C.T., Largactil and Amargyl all ineffective. Appeared recalcitrant. 3 April, 1959 put on imipramine 25 mg. t.d.s. Dramatic improvement within a few days. (Then became agitated but this soon abated on Sparine.) Recovery within five weeks treatment. Has remained home, well on maintenance doses four months.

Case No. 5. Age 43. Depressed in some degree for previous six years. Endogenous reactive type. Marital difficulties during that time. In-patient on two occasions in 1958. Given E.C.T., improved enough to go home. Never really well. Second time E.C.T. had to be terminated due to memory impairment. Veractil, Ritalin and Amargyl tried with little benefit. Re-admitted on 29 March, 1959. Very depressed. Given imipramine (Tofranil) daily. Improvement within few weeks leading to complete recovery from depression for first time for many years. Now stands up for herself and so relationships with husband have improved greatly. Home five months.

Case No. 6. Age 53. Many home worries. Manic depressive and menopausal. (Previous attack, 1953, when she attempted suicide by gas and aspirins.) Admitted very depressed following attempted suicide with Doriden. Steady, uneventful improvement on imipramine but dosage had to be raised to 100 mg. t.d.s. before recovery was attained. Home three months.

Case No. 7. Age 65. Manic depressive type. Numerous attacks of severe depression since the age of 48, and never really free from depression since then. On each admission improved with E.C.T. sufficiently to go home but always relapsed, usually with suicidal attempts. Present admission 20 March, 1959. Placed on imipramine. On 75 mg. t.d.s. recovered completely from her depression. Felt better than she had done for many years. Marvellous appetite, sleeping well. Home five months.

Case No. 8. Age 53. Menopausal depression of one year's duration, worse last two months. Admitted 5 May, 1959. (First admission.) Very depressed and agitated. On imipramine 50 mg., steady improvement. Developed diffuse rash which responded rapidly to Periten (antihistaminic). Recovery within a few weeks. Home for last three months.

Case No. 9. Age 30. Puerperal depression. T.B. during her adolescence, treated successfully now quiescent. Admitted 21 April, 1959. Depressed since birth of her first child three months previously. On admission was very depressed, suicidal inclinations. Insisted on departing four days later. Re-admitted 6 May, 1959. Condition unchanged. On imipramine gradually, improved and eventually recovered on 50 mg. t.d.s. Has been home very well for three months.

Case No. 10. Admitted 23 November, 1956, following attempted suicide, then aged 26. Schizo-affective psychosis. E.C.T. 60 treatments, a full course of chlorpromazine (Largactil) treatment (Blair and Brady, 1958) and later of trifluoperazine (Stelazine) had produced no substantial and sustained improvement. If ever sufficiently well to risk week-end leave she always returned worse and potentially suicidal.

In April, 1959, placed on imipramine. Little change to begin with but definite improvement as dose was raised to 75 mg. t.d.s. and then to 100 mg. t.d.s. Is now much improved. In an open ward for the first time since admission. Has ground and town parole. Goes home for week-ends. Manages housework and cooking. No relapse on return. Will probably recover before long. Has been made a voluntary patient.

Many more cases of interest could be cited but space forbids and the above varied cases represent a typical series of successful results.

Mode of Action

The mode in which the improvement took place is interesting, and can be summed up thus: the symptoms and qualitative feelings of the depressive syndrome gradually diminished and disappeared as an entity and not separately and were replaced by those of well-being and vitality which the patient experienced as her usual self. Patients did not experience feelings of euphoria.

Each patient seemed to react to a specific dosage and there was no obvious reason why some reacted on only 25 mg. t.d.s. and others required 100 mg. t.d.s. In some cases improvement was rapid and dramatic, in others not commencing for a few weeks and then only gradual. In twelve cases suffering from severe symptoms response to imipramine was so slow that E.C.T. had to be given as well, which in every case produced marked rapid improvement within a few treatments. It may well be that the use of E.C.T. in combination with imipramine is going to be at least as important as it is in combination with chlorpromazine (in the treatment of schizophrenics).

In cases who presented an agitated depression frequently imipramine reduced the depression but not the agitation. The additional medication of Amargyl (chlorpromazine with amylobarbitone), or Sparine tablets almost invariably soon resolved the agitation.

Imipramine seems to be a powerful stimulant of appetite and all patients put on weight and on "recovery" looked very healthy and vivacious. (None of them put on grossly excessive weight and adiposity as some cases do on chlorpromazine.) Indeed the change of appearance and expression was one of the most remarkable effects of the drug.

Patients suffering from insomnia associated with manic-depressive or endogenous depression nearly all recovered from this symptom as the depression lifted and did not need any night sedative. In cases of a neurotic type or arteriosclerotic type night sedatives frequently remained necessary.

One case who had "recovered" within a few weeks on imipramine had to have the tablets stopped owing to developing purpuric spots. Her depression immediately relapsed considerably. Another who went home depression-free stopped taking her maintenance tablets because she felt so well. Within two days she was in deep depression again and had to be re-admitted as an in-patient. Further imipramine produced recovery again and she is now at home on a maintenance dose.

It was found to be always essential to continue maintenance doses until the basic processes causing the depression have abated and patients must always be weaned gradually from the drug.

Side-Effects

Table VIII indicates the severe side-effects which occurred and their frequency. Apart from the major symptoms about to be described, atropine-like effects of a transient nature were common, e.g. nausea, disturbance of visual accommodation, headaches, and occasionally sweating. No case of photophobia occurred.

Table VIII

Side-Effects

Shakiness and agitation	9
Dizziness	7
Dryness of the mouth	16
Severe constipation	3
Erythematous rash	3
Epileptic fits	3
Purpuric patches on skin	2
Hypomania	2
Auditory hallucinations	1
Agranulocytosis	1

Shakiness and agitation were present in many cases in a mild and transient degree but then cleared up without any special medication. In the nine severe cases special medicative counteraction was required. In three cases the agitation was so bad that imipramine had to be abandoned altogether. The other six responded well and rapidly to Amargyl or Sparine tablets and the imipramine was continued in full doses.

Dizziness occurred in seven cases but this symptom was not connected with any marked decrease in blood pressure. The symptom cleared up spontaneously (probably as the result of an increased tolerance of the drug except in one case whose treatment had to be terminated). Amargyl, or Sparine, over a temporary period will often reduce and disperse this symptom.

Dryness of the mouth occurred in the early stages of treatment in many cases but in only 16 was it severe. In all cases it wore off within the course of several days and it presented no major problem.

Constipation in a mild degree was quite a common complaint but preoccupation with bowel function is, of course, one of the characteristics of depressive illnesses. It responded to routine aperients except in three cases in whom it was severe and temporarily required enemas. If the depression increased and disappeared the constipation did as well.

An erythematous urticarial rash occurred in three cases and in each of them was soon abolished by Periten tablets (anti-histaminic).

Imipramine is closely related to chlorpromazine in its chemical structure (see Fig. 1) and it seems that like chlorpromazine it is epilepticogenic to certain patients. Three patients (all elderly and with arteriosclerosis) had epileptic fits while on the drug—two had grand mals and one petit mals. However, in each of the grand mals cases only one fit occurred and in the petit mals only four sporadic fits.

Two cases developed purpuric spots. Blood counts and platelet counts were found to be normal in each case. They were thoroughly investigated by our visiting consultant physician. A diagnosis of purpura simplex was made in each case but this could not be definitely attributed to imipramine since one aged 72 was also on Doriden tablets for insomnia and the other, a chronic and resistive case, was also on Amargyl to counteract her agitation. Both cases recovered from their purpura on withdrawing all these drugs. Although it is not certain that the purpura was directly due to the imipramine these cases are included in the complications to draw attention to such a possibility.

Two manic-depressive cases whose depression was dispelled by imipramine veered into a mild hypomania. Imipramine was stopped and the hypomania soon disappeared and the patients "recovered".

One case of neurosis with depression treated by Imipramine recently developed auditory hallucinations. It seems probable that the drug was responsible for this symptom since the hallucinations (which had been very vivid) cleared up when the drug was withdrawn.

Blood pressure recordings were made every day. In some patients both the systolic and diastolic pressures varied very little throughout treatment. In others variations of 10 to 20 mm. Hg up or down occurred from day to day and in the large group of patients with a usual pressure of around 120/80 the systolic pressure sometimes dipped to the 90's or even 80's but the pulse pressure never dropped below 30 minutes. In cases with hypertension imipramine almost invariably reduced the blood pressure substantially and retained the reduction while treatment continued. No case of an acute hypotensive attack occurred. Instability of nervous regulation of blood pressure may have accounted for the feeling of dizziness experienced over a transitory period by certain patients when rising from a lying or sitting position. Changes in blood pressure were not correlated to the dose of the drug prescribed.

One case of agranulocytosis occurred. The patient, aged 57, a manic depressive, was admitted on 1 June 1959 (previous attack 15 years ago), and placed on imipramine which was gradually increased to 100 mg. t.d.s. On this her depression showed increasing improvement and had virtually recovered when, on 19 July, 1959, seven weeks after the commencement of treatment, she complained of a sore throat and developed a slight pyrexia. A blood count revealed agranulocytosis with a white cell count of 1,700. Next day the count was 1,500. The drug was, of course, withdrawn and a very rapid spontaneous recovery in the blood picture occurred. By 28 July, 1959 (i.e. eight days after commencement), the white count, which had increased each day, reached 8,000 with 69 per cent. neutrophils and 26 per cent. lymphocytes. This patient was also on Amargyl tablets for agitation, so it is not known whether the agranulocytosis was due to Tofranil alone or the combination.

No other significant change of blood count was found in any of the counts made either in the earlier or later stages of treatment. No definite eosinophilia occurred—possibly due to our scheme of gradual increase in dosage which I adopted.

In no case did even a suspicion of liver dysfunction occur.

Two cases of this series died during the investigation, one aged 72 from a severe haemorrhage from an old gastric ulcer, the other aged 96 from arteriosclerosis and cardiovascular degeneration. In neither case could the death be in any way attributed to imipramine.

As a matter of interest it is worth recording that one chronic neurotic patient determined to commit suicide did not swallow her tablets and having hoarded 44 of them took them all at once and informed us a few hours later. Her blood pressure sank to 90/60 and later to 85/50. She was treated by raising her bed and giving her repeated small doses of Digoxin. Her systolic blood pressure did not return to over 100 mm. for two days. However, apart from a feeling of weakness and light-headedness she did not complain of any particular distress or discomfort and recovered to her usual self uneventfully, except for an epileptic fit on the second night after the overdose.

Altogether in eight cases imipramine had to be terminated because of side-effects—three cases of extreme agitation and shakiness, one of severe dizziness, one of auditory hallucinosis, two of purpura, and one of agranulocytosis. It was not terminated in the cases who had epileptic fits.

Discussion

In 1957 Kuhn in Switzerland published the first paper on the treatment of depressive states by an aminodibenzyl derivative, imipramine hydrochloride (Tofranil). This drug is closely related in chemical composition to chlorpromazine (see Fig. 1) but its properties were found to be very different. Contrary to chlorpromazine, which is practically useless in the treatment of depression, imipramine was found to have a specific effect in dispelling depression. The pharmacologic way in which this is effected is still unknown but it has been designated a "thymoleptic" (mood regulating) drug.

Despite the well-recognized difficulties in assessing the potentialities of therapeutic measures for depression owing to the liability for spontaneous remissions, the present investigations indicate the definite potent antidepressant effects of imipramine, for the following reasons:

1. It has been effective in chronic cases of depression where all previous therapy has been ineffective.
2. In cases unsuitable for E.C.T. owing to serious physical illness, refusal to accept this form of treatment, very difficult veins, etc., it has frequently produced "recovery" and "much improvement".
3. A dramatic and rapid change following the introduction of imipramine occurred often enough to convince one that the change was due directly to the drug.
4. The results obtained from imipramine treatment on recent cases who would ordinarily have been treated by E.C.T. were at least as favourable as one could have anticipated from the latter treatment.
5. The convincing percentage results in the total material treated (Table III).
6. The subjective accounts of the patients successfully treated, especially those who had previously had E.C.T.

The present results substantiate those described by other writers (see references) who have all confirmed the marked anti-depressant effects of this drug. For instance, Lehmann *et al.* (1958) in 84 patients obtained the following results: Recovered 18 (21 per cent.), Much Improved 33 (40 per cent.), Improved 19 (23 per cent.), No Change 13 (15 per cent.), Worse 1 (1 per cent.);

Azima (1959) in 100 cases obtained marked improvement in 44 per cent. and moderate improvement in 38 per cent. Mann and MacPherson (1959) in 70 cases obtained "recovery" in 28·5 per cent., "much improvement" in 34·2 per cent., and "improvement" in 18·5 per cent.; and Fabio *et al.* in 50 cases recorded a "clinical remission" in 32 per cent. and "appreciable improvement" in 42 per cent. The individual case histories published by them are not less remarkable than those in this article. My results agree with those who have obtained the best results in the manic depressive and endogenous types. I have found that doses of 75 mg. and 150 mg. per day are effective (with patience) in most cases and that doses above 300 mg. per day are seldom necessary and this again is in agreement with observations by Kuhn (1958), Azima (1959) and Mann and MacPherson (1959), although Lehmann *et al.* (1958) and Sloane *et al.* (1959) used as much as 600 mg. per day in a few cases.

My findings regarding the general clinical mode of action of this drug on the depressive syndrome are in keeping with those described by Kuhn (1958) and it is not appropriate in this article to discuss its pharmacological mode of action. Fazio *et al.* (1958) reports the success of combined imipramine and E.C.T. therapies when neither has succeeded alone in two cases. Lehmann *et al.* (1958) refers to the necessity for using E.C.T. in combination with imipramine in severe cases where rapid result is required. In the present series 12 cases have required combined E.C.T. for this purpose.

Like chlorpromazine, imipramine has many side-effects. In the present series no seriously adverse side-effects occurred other than one case of agranulocytosis which rapidly recovered spontaneously. No previous case of agranulocytosis due to imipramine has been described, but this case had also been having Amargyl. It is not certain whether the two cases of purpura simplex were directly due to the drug. So far none of the authors of other articles has found any of them to be of any serious consequence, but Kuhn (1958) reported two transient cases of jaundice, and Lehmann *et al.* (1958) one case of myocardial infarction which might have been due to the drug. Lehmann had two cases of epileptic seizures due to imipramine. Mann and MacPherson (1959) describe an initial dramatic fall of blood pressure of up to 100 mm. in a few cases and the development of auditory hallucinations and delusions in one case. They also refer to immediate intolerance in which the patient is completely overwhelmed by marked jerkiness, dizziness, palpitations, tension, and agitation. The two severely agitated cases in my series were in this category. Lehmann (1958) found visual hallucinations as a complication in five cases. Steck *et al.* (1958) also had a similar case.

Side-effects are, of course, of the utmost import and insufficient cases have yet been reported to be certain whether any of them may be really dangerous. A gradual increase of dosage along the lines I have indicated will probably minimize the chances of serious complications but it would appear advisable, in the present stage of our knowledge, for patients wherever possible to be treated in hospital, and if they are treated as out-patients for them to be seen frequently at a clinic or by their practitioners.

It seems with reference to our up-to-date experience of imipramine we are in a stage similar to that of the early days of chlorpromazine treatment. Imipramine seems to be a potent anti-depressant drug with many side-effects, and further investigation is required before final conclusions are reached regarding its therapeutic potentialities, the best methods of counteracting its side-effects, and its place in the treatment of depression in relationship to E.C.T. and other anti-depressant drugs now appearing on the market (such as various

mono-amine oxidase inhibitors). A final assessment of the proportionate values of the various therapeutic measures for the treatment of depression will only be possible when further research has revealed the true aetiological changes occurring in this condition and the extent to which each therapeutic agent counteracts them. In the meantime it appears that imipramine (Tofranil) holds a place in the treatment of depression approximately equivalent to that held by chlorpromazine (Largactil) in the treatment of schizophrenia.

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